REMARKS

Claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 142-165, 167, 168, 179, 181-196 and 198-207 were pending in the present application. A Supplemental Amendment Under 37 C.F.R. § 1.111 filed April 27, 2009 ("Supplemental Amendment"), cancelled claims 192-196 and 198, and amended claims 62, 146, 155, 193 and 199, leaving claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 142-165, 167, 168, 179, 181-191 and 199-207 pending in this application. The present Listing of Claims is identical to that filed in the Supplemental Amendment.

The Office Action Summary indicates that claim 154 is rejected. However, the Detailed Action does not set forth a reason for rejecting claim 154

I. ENTRY OF DECLARATION AFTER FINAL REJECTION

Applicant respectfully submits that the Fourth Declaration of Mauro Magnani, Ph.D. Under 37 C.F.R. § 1.132 ("Fourth Magnani Declaration") submitted concurrently herewith should be entered in the file of the instant application and considered by the Examiner. 37 C.F.R. § 1.116(e) provides that an affidavit or other evidence submitted after a final rejection, but before or on the same date of filing an appeal, may be entered upon a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. The Fourth Magnani Declaration specifically addresses comments made by the Examiner in the final Office Action dated April 30, 2009 that were not made in the prior non-final Office Action dated July 8, 2008. In particular, the Fourth Magnani Declaration provides evidence of HIV Tat protein's expected loss of biological activity if one were to apply the acid exchange reaction of Sumner-Smith *et al.* before the lyophilization and resuspension step in Chang *et al.* In the present final Office Action, the Examiner has in her rejection under 35 U.S.C. § 103 alleged that one of ordinary skill would apply the acid exchange reaction of Sumner-Smith *et al.* before the lyophilization and resuspension step in Chang *et al.* to arrive at the claimed composition (see Office Action, page 10, lines 2-15). In the prior Office Action, however, the Examiner did not state that this was her believed order of how one skilled in the art would combine the teachings of the cited references. Instead, the Examiner's comments in the prior Office Action suggest the opposite order, *i.e.*, lyophilization and resuspension before acid exchange reaction. Specifically, in the prior Office Action (see pages 8-9), the Examiner first discussed the deficiencies of Chang *et al.*, then discussed the lyophilization process disclosed by Gu *et al.* and finally, discussed

Sumner-Smith *et al.*'s disclosure of exchanging TFA with a pharmaceutically acceptable carrier. Accordingly, Applicant believed, reasonably and in good faith, that the Examiner intended the teachings of the cited references to be combined in the order of using the lyophilization and resuspension step in Chang *et al.* before using the acid exchange reaction in Sumner-Smith *et al.* It was not until the instant final Office Action, in response to arguments made by the Applicant, that the Examiner indicated that her rejection contemplated that the acid exchange reaction in Sumner-Smith *et al.* would be performed by one skilled in the art before the lyophilization and resuspension step in Chang *et al.* In fact, the Examiner admits in the final Office Action (see page 10, line 2) that she "clarifies…the rejection." Accordingly, evidence in the Fourth Magnani Declaration was not earlier presented, because Applicant was not made aware of this aspect of the Examiner's rejection until the instant final Office Action, since the Examiner did not clarify the rejection until the instant final Office Action. Moreover, the Fourth Magnani Declaration is necessary to assist in demonstrating the nonobviousness of the claimed invention. For the foregoing reasons, the criteria of 37 C.F.R. § 1.116 are satisfied, and the Fourth Magnani Declaration should be entered and considered.

II. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 142-153, 155-162, 164, 165, 167, 168, 179, 181-186, 199-203, 205 and 206 are rejected under 35 U.S.C. § 103(a) ("Section 103(a)") as allegedly being obvious over Chang *et al.* (AIDS, 1997 Oct; 11(12):1421-31) in view of Sumner-Smith *et al.* (US 5,646,120), and as evidenced by Gu *et al.* (Sep. Technol., 1994, 4:258-260). Claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 114, 119, 142-153, 155-162, 164, 165, 167, 168, 179, 181-186 and 189 are rejected under Section 103(a) as allegedly being obvious over Chang *et al.* in view of Sumner-Smith *et al.* and Heiman *et al.* (web pages entitled "HIV Vaccines: Where are we Going?" http://www.niaid.nih.gov/daids/vaccine/1998nature.htm), as evidenced by Gu *et al.* Claims 62, 63, 65, 66, 68, 69, 89-97, 101-103, 105-111, 116, 117, 121, 122, 142-165, 167, 168, 179, 181-187, 190, 191, 204 and 207 are rejected under Section 103(a) as allegedly being obvious over Chang *et al.* in view of Sumner-Smith *et al.* and Vogel *et al.* ("A compendium of vaccine adjuvants and excipients." In: Powell MF, Newman MJ, editors. Vaccine design: The Subunit and Adjuvant Approach. Plenum, New York, 1995), as evidenced by Gu *et al.*

Claims 62, 63, 65, 66, 68, 69, 89-96, 98, 99, 101-103, 105-109, 111, 142-153, 155-162, 164, 165, 167, 168, 179 and 181-186 are rejected under Section 103(a) as allegedly being obvious over Chang *et al.* in view of Sumner-Smith *et al.* and Castignolles *et al.* (Vaccine, 1996 Oct; 14(14):1353-60), as evidenced by Gu *et al.* Claims 62, 63, 65, 66, 68, 69, 89-96, 98, 100-103, 105-109, 111, 142-153, 155-162, 164, 165, 167, 168 and 179-186 are rejected under Section 103(a) as allegedly being obvious over Chang *et al.* in view of Sumner-Smith *et al.* and Ramshaw *et al.* (J. Immunol. Methods, 1977; 18(3-4):251-5), as evidenced by Gu *et al.* Claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 112, 142-153, 155-162, 164, 165, 167, 168, 179-186 and 188 are rejected under Section 103(a) as allegedly being obvious over Chang *et al.* in view of Sumner-Smith *et al.* and Livingston *et al.* (J. Immunol., 1997 Aug 1; 159(3):1383-92), as evidenced by Gu *et al.* Claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 123, 142-153, 155-162, 164, 165, 167, 168, and 179-186 are rejected under Section 103(a) as allegedly being obvious over Chang *et al.* in view of Sumner-Smith *et al.* and Barry *et al.* (Clin. Pharmacokinet., 1997 Mar; 32(3):194-209), as evidenced by Gu *et al.* For the following reasons, Applicant respectfully disagrees.

1. Claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 142-153, 155-162, 164, 165, 167, 168, 179, 181-186, 199-230, 205 and 206 Are Not Obvious Over Chang *et al.* In View of Sumner-Smith *et al.*, And As Evidenced By Gu *et al.*

The Examiner alleges that Chang *et al.* teaches a composition comprising fully biologically active HIV Tat proteins, which are isolated by successive rounds of high-pressure liquid chromatography (HPLC) and ion-exchange chromatography (IEC), stored by lyophilization at -70°C and resuspended in degassed phosphate buffered saline (PBS) containing 0.1% bovine serum albumin (BSA) and 0.1 mM dithiothreitol (DTT) (see Office Action, page 6, second paragraph). Although the Examiner acknowledges that "Chang *et al.* does not expressly teach combining the Tat protein with a pharmaceutically acceptable carrier or excipient to form a composition," the Examiner alleges that "the lyophilization process disclosed by Chang *et al.* necessarily removes the acetonitrile, as evidenced by Gu *et al.*" (see Office Action, page 6, third paragraph). The Examiner also alleges that "Sumner-Smith *et al.* discloses that a peptide purified by HPLC and IEC is typically then treated to exchange the cleavage acid (e.g. TFA) with a pharmaceutically acceptable acid, such as acetic acid, to provide a water soluble salt of the peptide" (see Office Action, page 7, first paragraph, lines 1-4). The Examiner further alleges that Sumner-Smith *et al.* discloses that "[f]or therapeutic

use, proteins exhibiting pharmaceutical grade purity are combined with pharmaceutically acceptable carriers to generate compositions suitable for administration to patients" (see Office Action, page 7, lines 4-6). The Examiner then responds to Applicant's arguments made in the Amendment Under 37 C.F.R. § 1.111 filed January 8, 2009 by clarifying her rationale for the rejection, alleging that "[i]t would be immediately apparent and well within the knowledge of one skilled in the art to perform an acid exchange reaction *right after the column elution* for immediate removal of toxic organic solvents, but before lyophilization and resuspension…" (see Office Action, page 10, first paragraph; emphasis added). Further, the Examiner alleges that "Applicant has not provided any evidence distinguishing the claimed invention from the prior art disclosure of isolated HIV Tat protein in Chang *et al.*, in combination with the procedure for making a composition by combining with a pharmaceutically acceptable carrier or excipient as suggested by Gu *et al.* and Sumner-Smith *et al.*," and that "the 'wherein' clause reciting 'biologically active' and 'pharmaceutically acceptable for administration to a human is not given patentable weight because the intended use does not materially limit the claimed composition to a particular chemical structure that distinguishes over the prior art Tat protein composition" (see Office Action, paragraph bridging pages 10-11). Regarding the heparin affinity chromatography purification method disclosed in Chang *et al.*, the Examiner alleges that "[e]ven though there is no suggestion to avoid the use of PMSF in Chang *et al.*, applicant has admitted on the records, as evidenced by the two Magnani declarations…that it is common knowledge and routine experimentation in the art as of December 1, 1997 that a combination of purification steps should decrease levels of endotoxin in the resulting protein preparation and to avoid the use of PMSF in the process by purifying a protein at a pH or a temperature that inactivates proteases without harming the protein of interest" (see Office Action, page 7, second paragraph). For the following reasons, Applicant disagrees.

The relevant case law regarding obviousness was discussed in previously filed responses, for example, in the Amendment Under 37 C.F.R. § 1.111 filed May 1, 2007 ("May 1, 2007 Amendment") (see page 18), and the Amendment Under 37 C.F.R. § 1.114 filed May 8, 2008 ("May 8, 2008 Amendment") (see pages 18-19), and is not repeated herein.

Applicant respectfully submits that the Examiner has misconstrued the meaning of the claims and mischaracterized Applicant's arguments as well as the evidence of record. Firstly, Applicant addresses the meaning of the claims. Claim 62 expressly recites that the HIV Tat protein is biologically active, while claim 179 recites that the HIV Tat protein is in a "non-

oxidated form," and is thus biologically active. Contrary to the Examiner's contentions, the limitations of being biologically active and non-oxidated clearly impose a structural limitation on the claimed subject matter. As explained in the specification (see page 24, lines 21-25), when the HIV Tat protein is oxidized, the cysteine residues form disulfide bonds, changing the protein's conformation and causing loss of biological activity. This is clearly a structural change, which should be given patentable weight.

Moreover, the wherein clauses of claims 62 and 179 each specify "wherein said composition is pharmaceutically acceptable for administration to a human." Contrary to the Examiner's contentions, the wherein clauses state a feature that structurally limits the composition. As discussed and evidenced in documents already of record (see, *e.g.*, the Amendment Under 37 C.F.R. § 1.114 filed June 14, 2006 ("June 14, 2006 Amendment"), pages 16-18; and the May 1, 2007 Amendment, pages 14-15), the phrase "pharmaceutically acceptable for administration to a human" in claims 62 and 179 should be construed as meaning that the compositions are sufficiently safe for administration to human patients using the criteria for safety defined by regulatory agencies such as the Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA), *i.e.*, the compositions do not contain ingredients that the skilled artisan would know, based on knowledge common in the art, would result in denial of regulatory approval for marketing as a drug for humans. The recitation of the wherein clauses thus imposes a structural limitation to the claimed compositions in that they cannot contain ingredients (*e.g.*, unsafe substances such as acetonitrile, TFA, phenylmethylsulfonyl fluoride (PMSF), etc.) that would result in denial of regulatory approval for marketing as a drug for humans. Accordingly, the recitation requires the avoidance of such ingredients, and neither suggests nor makes optional the inclusion of such ingredients. Thus, the recitation must be given patentable weight in the determination of the scope of the claims.

As previously discussed in the Response Under 37 C.F.R. § 1.111 with Amendments filed December 13, 2005 (see pages 16-20), Chang *et al.* discloses two purification methods: (1) a first purification method involving reversed-phase high pressure liquid chromatography (RP-HPLC) and ion-exchange chromatography (IEC); and (2) a second purification method involving heparin affinity chromatography. As discussed in the June 14, 2006 Amendment (see pages 18-19), neither method yields a composition comprising a biologically active HIV Tat protein that is pharmaceutically acceptable for administration to a human, as recited in claims 62 and 179, even if combined with the secondary references put forth by the Examiner,

because the resulting composition would either contain TFA (if produced by the first purification method of Chang *et al.*) or PMSF (if produced by the second purification method of Chang *et al.*), and removal of TFA by the acid exchange reaction of Sumner-Smith *et al.*, as proposed by the Examiner, would *not* be expected to preserve the biological activity of the HIV Tat protein (see *infra*), and the Examiner has come forward with no reference that would give reason or motivation to avoid the use of PMSF in the second purification method, particularly in view of the prejudice in the art against the therapeutic use of biologically active HIV Tat protein.

Regarding the use of the acid exchange reaction of Sumner-Smith *et al.* to remove TFA, Applicant submits that the performance of the reaction would be expected to destroy the biological activity of an HIV Tat protein purified by RP-HPLC, even if the acid exchange reaction is performed before a lyophilization and resuspension step such as that described in Chang *et al.* The Examiner's attention is respectfully directed to the Fourth Magnani Declaration submitted concurrently herewith. Professor Magnani, an expert in the preparation of biologically active HIV Tat protein, states that the performance of the acid exchange reaction and consequent change of pH in an aqueous environment would promote loss of biological activity of the HIV Tat protein, regardless of whether the acid exchange reaction occurs just after RP-HPLC or just after lyophilization and resuspension (see Fourth Magnani Declaration, paragraph No. 3). As disclosed in the specification (see page 24, lines 21-25), the conformation and biological activity of a HIV Tat protein is strongly affected by the protein's cysteine rich region, such that when oxidized, the cysteine residues of the HIV Tat protein form intra- and inter-molecular disulfide bonds, thus modifying the conformation of the HIV Tat protein, causing aggregation and loss of biological activity. According to Professor Magnani, at an acidic pH, the HIV Tat protein is reduced and in a random coil conformation; as the pH increases, the protein tends to change its conformation, forming a non-biologically active structure stabilized by disulfide bonds (see Fourth Magnani Declaration, paragraph No. 4). Professor Magnani states that the acid exchange reaction described in Sumner-Smith *et al.*, while commonly used for peptides, is not commonly used for proteins (see Fourth Magnani Declaration, paragraph No. 5, lines 4-5). Professor Magnani explains that this is because, in general, proteins must retain their three-dimensional conformation in order to retain their biological activity, whereas short peptides often are not reliant on their three-dimensional conformation for their biological activity or can recover their biological activity more easily than larger proteins (see Fourth Magnani Declaration,

paragraph No. 5, lines 5-8). According to Professor Magnani, a person skilled in the art would understand that even a small increase in pH could cause a significant change in a protein's hydrogen exchange rate with water and changes in the protein conformation and biological activity, and that a change in pH from 3.3 to 5.8 causes an increase in the hydrogen exchange rate with water on the order of 250-fold for an HIV Tat protein, as determined by NMR spectroscopy, with consequent appearance of local conformation (see Fourth Magnani Declaration, paragraph No. 5, lines 9-16). Professor Magnani also states that one would expect that, under acid exchange conditions, the presence of a reducing agent would be necessary, although not necessarily sufficient, for the HIV Tat protein to maintain a non-oxidized, non-aggregated conformation and thus biological activity (see Fourth Magnani Declaration, paragraph No. 5, lines 16-19). According to Professor Magnani, if an HIV Tat protein is subjected to the acid exchange reaction of Sumner-Smith *et al.*, without the presence of a reducing agent, it is expected that the HIV Tat protein would lose biological activity (see Fourth Magnani Declaration, paragraph No. 5, lines 19-22). In addition, Professor Magnani states that, even in the presence of a reducing agent (which is not taught by Sumner-Smith *et al.*), there is no way to predict whether, and thus no expectation that, the biological activity of the HIV Tat protein would be preserved (see Fourth Magnani Declaration, paragraph No. 5, lines 22-24). Professor Magnani thus concludes that if the acid exchange reaction described by Sumner-Smith *et al.* were to be applied to an HIV Tat protein purified by the RP-HPLC method of Chang *et al.*, the change in the pH of the HIV Tat protein in an aqueous environment would not be expected to preserve the biological activity of the HIV Tat protein (see Fourth Magnani Declaration, paragraph No. 5, lines 24-28). Professor Magnani further states that a subsequent lyophilization step, as disclosed in Chang *et al.*, does not entail any steps that would be expected to restore the native conformation and thus biological activity of the HIV Tat protein (see Fourth Magnani Declaration, paragraph No. 5, lines 28-30).

The Examiner's clarification of the order of performing the acid exchange reaction in Sumner-Smith *et al.* before the lyophilization and resuspension step in Chang *et al.* makes no difference, since it is the *exposure to acetic acid and consequent change of pH in an aqueous environment* that is expected to destroy the biological activity of the HIV Tat protein (see also Fourth Magnani Declaration at paragraph No. 5; see also Third Declaration of Mauro Magnani, Ph.D. Under 37 C.F.R. § 1.132 filed January 8, 2009, paragraph No. 8). None of the other references cited by the Examiner provide a way to remove TFA without losing

biological activity of the HIV Tat protein, and none of the other references are alleged by the Examiner to do so; thus, none of the cited references remedy the deficiencies of the first purification method of Chang *et al.*

While the above discussion sufficiently shows that Sumner-Smith *et al.*'s acid exchange reaction does not remedy the deficiency of Chang *et al.*'s first purification method, there is yet an additional reason why Sumner-Smith *et al.*'s acid exchange reaction does not remedy the deficiency of Chang *et al.*'s first purification method. Under *KSR*, it is important to identify a reason why one would combine the teachings of the different references. *See KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741, U.S.P.Q.2d 1385, 1396 (2007). Here, the Examiner's reason to use the acid exchange reaction of Sumner-Smith *et al.* in order to remove TFA from the Tat composition obtained by the first purification method of Chang *et al.* is based on the alleged desire of one of ordinary skill in the art to administer a biologically active HIV Tat protein to a human. This reason, however, cannot stand, since it is contrary to the common understanding at the time of the invention that a biologically active HIV Tat protein would be harmful when administered to a human. As previously discussed in the May 8, 2008 Amendment (see pages 20-23), the Third Declaration of Barbara Ensoli, M.D., Ph.D. Under 37 C.F.R. § 1.132 ("Third Ensoli Declaration") shows the prejudice in the prior art and the clear skepticism and disbelief by experts in the art that taught away from administration of a biologically active HIV Tat protein to a human due to the knowledge that a biologically active HIV Tat protein had many activities that were believed to result in harmful health effects (see paragraph No. 17). Accordingly, one of ordinary skill in the art would have no reason to formulate a composition comprising a biologically active HIV Tat protein, such as that disclosed in Chang *et al.*, for administration to a human by removing TFA from the composition with the acid exchange reaction disclosed by Sumner-Smith *et al.* in order to render the composition pharmaceutically acceptable for administration to a human. *See KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1741.

In the Examiner's "Response to Arguments" section of the Office Action (see page 12, second paragraph), the Examiner discounts the above reasons for finding the claims nonobvious by making two erroneous statements. Firstly, the Examiner states that "Applicant's argument regarding the lack of reason for modifying an isolated Tat protein to be suitable for administration to a human is solely based on the inventor, Dr. Ensoli's opinion that Tat protein had many activities that were believed to result in harmful health effects" (see Office Action, page 12, second paragraph, lines 1-4). Applicant respectfully questions

how the Examiner could characterize Applicant's argument as "solely based" on Dr. Ensoli's opinion. Applicant's argument was based on the Third Ensoli Declaration, which was accompanied by 42 references as supporting Exhibits, as evidence of the concern in the art and bases therefore that a biologically active HIV Tat protein would be harmful when administered to a human. Moreover, the Third Ensoli Declaration did not merely "express[] doubt about the harmful health effects of the protein" (see Office Action, page 12, line 6), but, rather, showed by way of evidence in the accompanying Exhibits 2-43 the many believed harmful health effects of administering a biologically active HIV Tat protein (see, *e.g.*, paragraph Nos. 3-12). Specifically, the Third Ensoli Declaration showed that as of December 1, 1997, it was well known to one of ordinary skill in the art that a biologically active HIV Tat protein (i) plays an essential role in HIV replication and viral gene expression and contributes to the pathogenesis of HIV, and thus, that the administration of a biologically active HIV Tat protein to humans would be undesirable (see paragraph No. 4); (ii) induces immune hyperactivation, which was speculated to be critical for the maintenance of the HIV infectious process and was thought possibly to contribute to development of cancer in AIDS (see paragraph No. 5); (iii) protects HIV-infected T cells from apoptosis (leading to disease progression) but induces apoptosis in uninfected T cells (leading to severe immune suppression) (see paragraph No. 6); (iv) protects uninfected T cells from apoptosis, perhaps contributing to cancer development in HIV-infected individuals (see paragraph No. 7); (v) has immunosuppressive effects (see paragraph No. 8); (vi) increases production of a number of inflammatory cytokines that adversely affect the functions of uninfected cells, which had been suggested as contributing to the pathogenesis of AIDS and AIDS-associated disorders (see paragraph No. 9); (vii) causes damage to vital organs such as the central nervous system (see paragraph No. 10); (ix) acts as an exogenous growth factor that promotes the growth of AIDS-Kaposi's sarcoma cells (see paragraph No. 11); and (x) enhances the chemotactic and invasive behaviors of monocytes, possibly recruiting monocytes into extravascular tissues, a process which was speculated to contribute to the destruction of tissues and cellular architecture seen in patients with AIDS (see paragraph No. 12). The publications discussed in paragraph Nos. 3-12 of the Third Ensoli Declaration are evidence of prejudice in the prior art against the therapeutic use of biologically active Tat and thus the lack of reason or motivation in the art to formulate a biologically active HIV Tat protein in a composition that would be pharmaceutically acceptable for administration to a human. These publications and the Third Ensoli Declaration thus evidence the lack of reason in the prior art to modify the

purification methods of Chang *et al.* to include a biologically active HIV Tat protein in a composition that would be pharmaceutically acceptable for administration to a human.

Moreover, the knowledge in the art that a biologically active HIV Tat protein had many activities that were believed to result in harmful health effects, as evidenced by the Third Ensoli Declaration, made it unexpected that a composition comprising a biologically active HIV Tat protein would be beneficial and safe when administered to humans (see Third Ensoli Declaration, paragraph No. 17). Contrary to the prejudice in the art, results of a human clinical trial using a biologically active HIV Tat protein showed that the biologically active HIV Tat protein was safe and well tolerated in all subjects in the trial (see paragraph Nos. 6-10 of the Second Declaration of Barbara Ensoli, M.D., Ph.D. Under 37 C.F.R. § 1.132 filed May 1, 2007). The Third Ensoli Declaration also identifies a number of publications that are evidence of skepticism by experts once the claimed invention was disclosed (see paragraph Nos. 13-16). Evidence of unexpected results and skepticism by experts are secondary considerations of nonobviousness that must be considered in determining whether the claimed invention is obvious. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18; see also Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Federal Register, Vol. 72, No. 195, October 10, 2007, page 57527, paragraph bridging cols. 1-2. Applicant submits that such secondary considerations are sufficient both to rebut any *prima facie* case of obviousness made by the Examiner and to demonstrate the nonobviousness of the claimed invention.

The second erroneous statement made by the Examiner on page 12, second paragraph of the Office Action, refers to the Examiner's mistaken contention that the cited prior art (presumably, Sumner-Smith *et al.*, referred to on page 7, first paragraph of the Office Action) teaches combining purified proteins with pharmaceutically acceptable carriers to generate compositions suitable for administration to patients. As discussed above, Sumner-Smith *et al.* teaches combining therapeutic oligopeptides, not proteins, with pharmaceutically acceptable carriers to generate compositions suitable for administration to a patients.

Regarding the Tat composition obtained by the second purification method of Chang *et al.*, as discussed above, the presence of PMSF in the Tat composition obtained by the second purification method of Chang *et al.* renders the composition not pharmaceutically acceptable for administration to a human (see Second Declaration of Shayne Gad, Ph.D. Under 37 C.F.R. § 1.132 filed June 14, 2006 at paragraph No. 7). While the Examiner admits

that there is no suggestion in Chang *et al.* to avoid the use of PMSF, the Examiner alleges that "applicant has admitted on the record, as evidenced by the two Magnani declarations…that it is common knowledge and routine experimentation in the art as of 1 December 1997 that a combination of purification steps should decrease levels of endotoxin in the resulting protein preparation and to avoid the use of PMSF in the process by purifying a protein at a pH or a temperature, e.g. near 0°C, that inactivates proteases without harming the protein of interest" (see Office Action, page 7, second paragraph). In response, Applicant respectfully submits that the Examiner has again mischaracterized the Declaration of Mauro Magnani, Ph.D. Under 37 C.F.R. § 1.132 filed May 1, 2007 and the Supplemental Declaration of Mauro Magnani, Ph.D. Under 37 C.F.R. § 1.132 filed October 22, 2007, and Applicant's arguments based thereon. First, the two Magnani declarations were submitted to show that a person skilled in the art as of December 1, 1997, based on the teaching of the specification and knowledge common in the art as of December 1, 1997, and using only routine experimentation, *could* obtain a composition comprising a biologically active HIV Tat protein and being pharmaceutically acceptable for administration to a human, were such a person so motivated. However, neither Magnani declaration supports the Examiner's proposition that a person of ordinary skill in the art *would* be motivated to do so. Nevertheless, the Examiner fails to appreciate the difference and further ignores the evidence set forth in the Third Ensoli Declaration, that one of ordinary skill in the art as of December 1, 1997 would *not* be so motivated, *i.e.*, that one would not have reason, except as gleaned from the instant application, to modify the known procedures for obtaining a biologically active HIV Tat protein (such as those described in Chang *et al.*) in order to obtain a biologically active HIV Tat protein in a composition that would be pharmaceutically acceptable for administration to a human, because of the concern in the art that a biologically active HIV Tat protein would be harmful when administered to a human. Thus, the Examiner has failed to appreciate a distinction that *KSR* mandates be paid attention to: whether there is reason (or motivation) to make the combination of teachings necessary to achieve the claimed invention. *KSR,* 127 S.Ct. at 1741 ("Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does"). The Examiner has failed to discern the difference between what one could do *if* one were so motivated, and *whether* one would be so

motivated. Applicant's remarks and evidence have shown that one could obtain a biologically active HIV Tat protein in a composition that is pharmaceutically acceptable for administration to a human, if one were so motivated (*e.g.*, as taught by the instant specification), but that one would *not* be so motivated in the absence of Applicant's teachings, and especially in view of the prejudice in the prior art against the formulation of a biologically active HIV Tat protein in a composition that would be pharmaceutically acceptable for administration to a human, as evidenced by the Third Ensoli Declaration. Hindsight should be avoided in determining obviousness. The Supreme Court in *KSR* citing *Graham*, upheld the principle of *avoiding hindsight bias* and cautioned courts to *guard against reading into the prior art the teachings of the invention in issue*. 127 S.Ct. at 1742,

For the foregoing reasons, Applicant submits that claims 62 and 179 and their dependent claims are not obvious over Chang *et al*. in view of Sumner-Smith *et al*., as evidenced by Gu *et al*. Withdrawal of this Section 103(a) rejection is respectfully requested.

For clarity of the record, Applicant wishes to address certain additional remarks made by the Examiner in the Office Action dated April 30, 2009:

In the paragraph spanning pages 8-9 of the Office Action, the Examiner contends that Applicant later discounts Applicant's statement that methods for modifying the procedures disclosed in the specification so as to avoid acetonitrile, TFA and PMSF are well known in the art, by contending that the Third Ensoli Declaration shows the prejudice in the art and clear skepticism and disbelief by experts in the art that taught away from administration of a biologically active HIV Tat protein due to knowledge that biologically active Tat protein had many activities that were believed to result in harmful health effects. As discussed above, the Examiner has mischaracterized the evidence set forth in the two Magnani declarations and the Third Ensoli Declaration. On one hand, the two Magnani declarations were submitted to show that a person skilled in the art as of December 1, 1997, based on the teaching of the specification and knowledge common in the art as of December 1, 1997, and using only routine experimentation, *could* obtain a composition comprising a biologically active HIV Tat protein that was pharmaceutically acceptable for administration to a human, if such a person were so motivated. On the other hand, the Third Ensoli Declaration was submitted to show that such a person would not be so motivated, by showing the prejudice in the prior art and the clear skepticism and disbelief by experts in the art that taught away from administration of a biologically active HIV Tat protein to a human due to the knowledge that a biologically active HIV Tat protein had many activities that were believed to result in

harmful health effects. The two Magnani declarations addressed the issue of enablement, whereas the Third Ensoli Declaration addressed the issue of nonobviousness. Applicant submits that the Examiner has confused the two standards and what is shown by the evidence in the different sets of declaration.

Regarding Applicant's remarks and the Third Magnani Declaration showing that the phase separation method of Gu *et al.* would not be applicable for the extraction of an HIV Tat protein, the Examiner states that the phase separation method is "irrelevant to the rejection at issue because it is an extraneous fact" (see Office Action, paragraph spanning pages 3-4 and sentence spanning pages 11-12). In response, Applicant respectfully points out that she is therefore unaware of the reasons for the Examiner's repeated description of the phase separation method in the Office Action dated July 8, 2008 at the bottom of page 8, and in the instant Office Action at page 6, bottom paragraph.

2. Claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 114, 119, 142-153, 155-162, 164, 165, 167, 168, 179, 181-186 and 189 Are Not Obvious Over Chang *et al.* In View of Sumner-Smith *et al.* and Heiman *et al.*, As Evidenced By Gu *et al.*

As discussed above, Chang *et al.* does not teach or suggest a biologically active HIV Tat protein in a composition that is rid of all ingredients, such as acetonitrile, TFA and PMSF, that would render the composition not pharmaceutically acceptable for administration. The Examiner's reason to use the acid exchange reaction of Sumner-Smith *et al.* in order to remove TFA from the Tat composition obtained by the first purification method of Chang *et al.* is based on the alleged desire of one of ordinary skill in the art to administer a biologically active HIV Tat protein to a human, which cannot stand since it directly contravenes the evidence in the Third Ensoli Declaration, which shows the prejudice in the prior art and clear skepticism and disbelief by experts in the art that taught away from administration of biologically active HIV Tat protein in humans due to the knowledge that biologically active HIV Tat protein had many activities that were believed to result in harmful health effects. Moreover, subjecting the Tat composition of the first purification method of Chang *et al.* to the acid exchange reaction of Sumner-Smith *et al.* is expected to destroy the biological activity of the HIV Tat protein, thus failing to yield a composition comprising a biologically active HIV Tat protein that is pharmaceutically acceptable for administration to a human (see Third Magnani Declaration, paragraph No. 8). Regarding the Tat composition obtained from the second purification method of Chang *et al.* that is tainted with PMSF and thus not

pharmaceutically acceptable for administration to a human, the Examiner has not come forward with any reason for one of ordinary skill in the art to avoid the use of PMSF, particularly in view of the prejudice in the art against the therapeutic use of biologically active HIV Tat protein.

Heiman *et al.* does not cure the deficiencies of any of these references, because Heiman *et al.* also does not give reason to formulate biologically active HIV Tat protein in a composition that is pharmaceutically acceptable for administration to a human; thus, Heiman *et al.* does not provide the missing motivation. While Heiman discloses a number of recent research findings that influence HIV vaccine design (see Heiman *et al.*, first page, first paragraph), Heiman does not teach or suggest an HIV Tat protein, much less teach or suggest a biologically active HIV Tat protein in a composition that is pharmaceutically acceptable for administration to a human. Again, the Examiner relies on an unfounded belief that one of ordinary skill in the art would be motivated to use the teaching of Heiman *et al.* to further modify the Tat composition of Chang *et al.* in order to arrive at a Tat composition which is pharmaceutically acceptable for administration to a human. This is contradictory to the evidence presented in the Third Ensoli Declaration that one of ordinary skill in the art would not be motivated to formulate a biologically active HIV Tat protein into a composition that is pharmaceutically acceptable for administration to a human. Thus, there is no suggestion or motivation or any other reason based on Chang *et al.*, alone or in combination with any of the other references cited in support of the Section 103(a) rejections, to modify the purification methods of Chang *et al.* so that acetonitrile, TFA and PMSF, that are not pharmaceutically acceptable for administration to a human, are avoided. It is respectfully submitted that this Section 103(a) rejection is in error and withdrawal of the rejection is respectfully requested.

3. Claims 62, 63, 65, 66, 68, 69, 89-97, 101-103, 105-111, 116, 117, 121, 122, 142-165, 167, 168, 179, 181-187, 190, 191, 204 and 207 Are Not Obvious Over Chang *et al.* In View of Sumner-Smith *et al.* and Vogel *et al.*, As Evidenced By Gu *et al.*

For the reasons discussed above, Applicant submits that claims 62 and 179, as well as their dependent claims, are not obvious over Chang *et al.* in view of Sumner-Smith *et al.*, as evidenced by Gu *et al.* Vogel *et al.* does not cure the deficiencies of any of these references, because Vogel *et al.* also does not teach or suggest or give reason to use a composition comprising a biologically active HIV Tat protein that is pharmaceutically acceptable for administration to a human; thus, Vogel *et al.* does not provide the missing motivation.

Instead, Vogel discloses a wide variety (*i.e.*, compendium) of organic and inorganic compounds that are useful for improving the immunogenicity of vaccines (see Vogel, first page, first paragraph). Again, the Examiner relies on an unfounded belief that one of ordinary skill in the art would be motivated to use the teaching of Vogel *et al.* to further modify the Tat composition of Chang *et al.* in order to arrive at a Tat composition which is pharmaceutically acceptable for administration to a human. This is contradictory to the evidence presented in the Third Ensoli Declaration that one of ordinary skill in the art would not be motivated to formulate a biologically active HIV Tat protein into a composition that is pharmaceutically acceptable for administration to a human. Thus, there is no suggestion or motivation or any other reason based on Chang *et al.*, alone or in combination with any of the other references cited in support of the Section 103(a) rejections, to modify the purification methods of Chang *et al.* so that acetonitrile, TFA and PMSF, that are not pharmaceutically acceptable for administration to a human, are avoided. It is respectfully submitted that this Section 103(a) rejection is in error and withdrawal of the rejection is respectfully requested.

4. Claims 62, 63, 65, 66, 68, 69, 89-96, 98, 99, 101-103, 105-109, 111, 142-153, 155-162, 164, 165, 167, 168, 179 and 181-186 Are Not Obvious Over Chang *et al.* In View of Sumner-Smith *et al.* and Castignolles *et al.*, As Evidenced By Gu *et al.*

For the reasons discussed above, Applicant submits that claims 62 and 179, as well as their dependent claims, are not obvious over Chang *et al.* in view of Sumner-Smith *et al.*, as evidenced by Gu *et al.* Castignolles *et al.* does not cure the deficiencies of any of these references, because Castignolles *et al.* also does not teach or suggest or give reason to use a composition comprising a biologically active HIV Tat protein that is pharmaceutically acceptable for administration to a human; thus, Castignolles *et al.* does not provide the missing motivation. Instead, Castignolles discloses a new family of biovectors that are useful for enhancing the immunogenicity of rabies antigens (see Castignolles, Title). Again, the Examiner relies on an unfounded belief that one of ordinary skill in the art would be motivated to use the teaching of Castignolles *et al.* to further modify the Tat composition of Chang *et al.* in order to arrive at a Tat composition which is pharmaceutically acceptable for administration to a human. This is contradictory to the evidence presented in the Third Ensoli Declaration that one of ordinary skill in the art would not be motivated to formulate a biologically active HIV Tat protein into a composition that is pharmaceutically acceptable for administration to a human. Thus, there is no suggestion or motivation or any other reason

based on Chang *et al.*, alone or in combination with any of the other references cited in support of the Section 103(a) rejections, to modify the purification methods of Chang *et al.* so that acetonitrile, TFA and PMSF, that are not pharmaceutically acceptable for administration to a human, are avoided. It is respectfully submitted that this Section 103(a) rejection is in error and withdrawal of the rejection is respectfully requested.

5. Claims 62, 63, 65, 66, 68, 69, 89-96, 98, 100-103, 105-109, 111, 142-153, 155-162, 164, 165, 167, 168 and 179-186 Are Not Obvious Over Chang *et al.* In View of Sumner-Smith *et al.* and Ramshaw *et al.*, As Evidenced By Gu *et al.*

As a preliminary matter, claim 180 was cancelled in the Amendment Under 37 C.F.R. § 1.111 filed January 8, 2009 ("January 8, 2009 Amendment"). The rejection of cancelled claim 180 is in error and should be withdrawn.

For the reasons discussed above, Applicant submits that claims 62 and 179, as well as their dependent claims, are not obvious over Chang *et al.* in view of Sumner-Smith *et al.*, as evidenced by Gu *et al.* Ramshaw *et al.* does not cure the deficiencies of any of these references, because Ramshaw *et al.* also does not teach or suggest or give reason to use a composition comprising a biologically active HIV Tat protein that is pharmaceutically acceptable for administration to a human; thus, Ramshaw *et al.* does not provide the missing motivation. Instead, Ramshaw discloses that, on a dose basis, antigen coupled to autologous red blood cells is 1,000 to 10,000-fold more efficient at inducing an antibody response than the soluble form (see Ramshaw, Abstract). Again, the Examiner relies on an unfounded belief that one of ordinary skill in the art would be motivated to use the teaching of Ramshaw *et al.* to further modify the Tat composition of Chang *et al.* in order to arrive at a Tat composition which is pharmaceutically acceptable for administration to a human. This is contradictory to the evidence presented in the Third Ensoli Declaration that one of ordinary skill in the art would not be motivated to formulate a biologically active HIV Tat protein into a composition that is pharmaceutically acceptable for administration to a human. Thus, there is no suggestion or motivation or any other reason based on Chang *et al.*, alone or in combination with any of the other references cited in support of the Section 103(a) rejections, to modify the purification methods of Chang *et al.* so that acetonitrile, TFA and PMSF, that are not pharmaceutically acceptable for administration to a human, are avoided. It is respectfully submitted that this Section 103(a) rejection is in error and withdrawal of the rejection is respectfully requested.

6. Claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 112, 142-153, 155-162, 164, 165, 167, 168, 179-186 and 188 Are Not Obvious Over Chang *et al.* In View of Sumner-Smith *et al.* and Livingston *et al.*, As Evidenced By Gu *et al.*

As a preliminary matter, claim 180 was cancelled in the January 8, 2009 Amendment. The rejection of cancelled claim 180 is in error and should be withdrawn.

For the reasons discussed above, Applicant submits that claims 62 and 179, as well as their dependent claims, are not obvious over Chang *et al.* in view of Sumner-Smith *et al.*, as evidenced by Gu *et al.* Livingston *et al.* does not cure the deficiencies of any of these references, because Livingston *et al.* also does not teach or suggest or give reason to use a composition comprising a biologically active HIV Tat protein that is pharmaceutically acceptable for administration to a human; thus, Livingston *et al.* does not provide the missing motivation. Instead, Livingston *et al.* discloses that "lipopeptides safely induce specific CTL activity in humans of such magnitude and persistence as to be of potential therapeutic significant" (see Livingston *et al.*, Abstract, last three lines). Again, the Examiner relies on an unfounded belief that one of ordinary skill in the art would be motivated to use the teaching of Livingston *et al.* to further modify the Tat composition of Chang *et al.* in order to arrive at a Tat composition which is pharmaceutically acceptable for administration to a human. This is contradictory to the evidence presented in the Third Ensoli Declaration that one of ordinary skill in the art would not be motivated to formulate a biologically active HIV Tat protein into a composition that is pharmaceutically acceptable for administration to a human. Thus, there is no suggestion or motivation or any other reason based on Chang *et al.*, alone or in combination with any of the other references cited in support of the Section 103(a) rejections, to modify the purification methods of Chang *et al.* so that acetonitrile, TFA and PMSF, that are not pharmaceutically acceptable for administration to a human, are avoided. It is respectfully submitted that this Section 103(a) rejection is in error and withdrawal of the rejection is respectfully requested.

7. Claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 123, 142-153, 155-162, 164, 165, 167, 168 and 179-186 Are Not Obvious Over Chang *et al.* In View of Sumner-Smith *et al.* and Barry *et al.*, As Evidenced By Gu *et al.*

As a preliminary matter, claim 180 was cancelled in the January 8, 2009 Amendment. The rejection of cancelled claim 180 is in error and should be withdrawn.

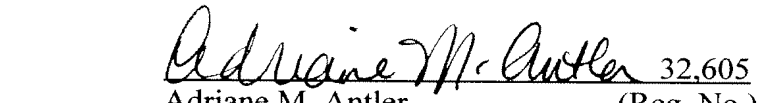
For the reasons discussed above, Applicant submits that claims 62 and 179, as well as their dependent claims, are not obvious over Chang *et al.* in view of Sumner-Smith *et al.*, as evidenced by Gu *et al.* Barry *et al.* does not cure the deficiencies of any of these references, because Barry *et al.* also does not teach or suggest or give reason to use a composition comprising a biologically active HIV Tat protein that is pharmaceutically acceptable for administration to a human; thus, Barry *et al.* does not provide the missing suggestion. Instead, Barry *et al.* discloses that "[a]dministration of protease inhibitors…in combination with other drugs does raise a number of pharmacokinetic issues for patients with HIV disease" (see Barry *et al.*, sentence spanning pages 194-195). Again, the Examiner relies on an unfounded belief that one of ordinary skill in the art would be motivated to use the teaching of Barry *et al.* to further modify the Tat composition of Chang *et al.* in order to arrive at a Tat composition which is pharmaceutically acceptable for administration to a human. This is contradictory to the evidence presented in the Third Ensoli Declaration that one of ordinary skill in the art would not be motivated to formulate a biologically active HIV Tat protein into a composition that is pharmaceutically acceptable for administration to a human. Thus, there is no suggestion or motivation or any other reason based on Chang *et al.*, alone or in combination with any of the other references cited in support of the Section 103(a) rejections, to modify the purification methods of Chang *et al.* so that acetonitrile, TFA and PMSF, that are not pharmaceutically acceptable for administration to a human, are avoided. It is respectfully submitted that this Section 103(a) rejection is in error and withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicant respectfully requests entry of the remarks made herein into the file history of the present application. Withdrawal of the Examiner's rejections and an allowance of the application are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: October 29, 2009



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